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CLINICAL RESEARCH

Risk factors for mortality in patients with mediastinitis after cardiac surgery

Évaluation des facteurs de mortalité associés aux médiastinites après chirurgie cardiaque

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KEYWORDS
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Summary
Background. — Patients with mediastinitis after cardiac surgery have higher morbidity and mortality.
Aims. — Describe the characteristics of patients with mediastinitis, determine the mortality within one month, and assess the risk factors associated with mortality.
Methods. — Retrospective cohort study including all adult patients with mediastinitis during the 2002—2006 period at the Nantes University Hospital. Multivariate analysis by logistic regression and Kaplan-Meier curve of survey were done.
Results. — Nearly 5574 patients were operated during the study period, with a mediastinitis incidence rate of 0.7%, 28 patients (72%) had coronary artery bypass graft. The mortality rate increased from de 12.8% during hospital stay to 20.5% within one year. Only two deaths were

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associated with mediastinitis. The occurrence of a co-infection was the only independent risk factor associated with mortality (OR 13, $P < 0.04$). The instantaneous risk of death was increased by 7 in patient with co-infection, particularly mechanical ventilator-associated pneumonia (CR 1,97).
Conclusion. — Mortality varied according to the duration of surveillance, and mediastinitis was not the major cause of death. Mechanical ventilator-associated pneumonia after mediastinitis increases the mortality and needs specific prevention.

MOTS CLÉS
Médiastinite ;
Mortalité ;
Staphylococcus aureus ;
Facteur de risque ;
Survie

Résumé
Contexte. — Les patients pris en charge pour médiastinite ont une morbidité et une mortalité plus élevées que ceux n'ayant pas de complication infectieuse.
Objectifs. — Analyser les caractéristiques des patients ayant présenté une médiastinite, mesurer la mortalité à 30 jours et définir les facteurs de mortalité associés.
Méthodes. — Nous avons réalisé une enquête de cohorte rétrospective dans le service de chirurgie cardiothoracique du CHU de Nantes incluant les patients adultes réopérés pour médiastinite entre avril 2002 et août 2006. L'analyse statistique comprenait une régression logistique et une analyse de survie, selon Kaplan-Meier afin de mesurer la probabilité de survie à un mois et à un an.
Résultats. — Sur les 5574 patients opérés, 39 patients ont développé une médiastinite (0,7 %) ; 28 patients (72 %) avaient bénéficié d'un pontage coronarien. Le taux de mortalité était de 12,8 % pendant l'hospitalisation (dont 2,6 % à j30) et de 20,5 % à un an. Seul deux décès étaient imputables à la médiastinite. Parmi les facteurs étudiés, seule la présence d'une coinfection était associée au risque de décès (OR 13, $P < 0,04$). Le risque instantané de décès était multiplié par un facteur 7 chez les patients présentant une infection associée, notamment une pneumopathie (CR 1,97).
Conclusion. — Le taux de mortalité variait en fonction de la durée de suivi des patients, la médiastinite n'étant pas la cause principale de décès. Les pneumopathies survenant au décours d'une médiastinite aggraveraient le taux de mortalité.

Introduction

Mediastinitis is a serious infectious complication of cardiac surgery affecting 0.25 to 2.9% of patients in the poststernotomy period [1—3]. It prolongs hospitalisation, adds to the financial burden of medical care [4,5] and is associated with a higher risk of mortality [2,6].

The risk factors associated with mediastinitis of the patients undergoing surgery in our Institute were analysed and allowed us to better orient our prevention programs [1]. However, the relationship between mediastinitis and death is still poorly evaluated. Excess mortality persists long-term even if both diagnosis and treatment are satisfactory and if the in-hospital outcome is positive [6,7]. The risk of mortality has already been evaluated, either by comparing closed drainage with Redon-type vacuum drains versus irrigation-drainage [8] or by identifying peri-operative risk factors in patients hospitalised in the Intensive Care Unit (ICU) [9]. A clearer definition of these risk factors could improve management of patients developing post-surgical mediastinitis and prevent the related excess mortality. The primary endpoints of this study were to analyse the characteristics of patients presenting with mediastinitis, measure mortality at 30 days and define the associated risk factors.

Materials and methods

Study population

This cohort study was conducted in the Chest and Heart Surgery Department of the Institut du Thorax at the Laënnec Hospital (Nantes Teaching Hospital Centre or CHU), where 1300 adult cardiac surgery procedures are performed every year. All cases of re-operation for mediastinitis in adult patients between April 2002 and July 2006 were analysed and included in the study. The outcome of patients was recorded in August 2007 to obtain a minimum follow-up of one year. The exhaustive list of cases was obtained from the Bacteriology-Hygiene Department which has coordinated continuous monitoring of surgical wound infections since 2002. Each case of suspected mediastinitis was reported on an infection control form by the operating theatre Manager, then discussed in the weekly multi-disciplinary staff meeting. A diagnosis of mediastinitis was based on the need for sternal re-operation and insertion of an irrigation-drainage system and/or combined with positive mediastinal sample bacteriology cultures or macroscopic appearance of mediastinitis. Patients with strictly cutaneous and sub-cutaneous infection were not included, their infection being defined as superficial.

Data collection

The criteria explored in our study included:
- the demographic data of the patients and their history;
- peri-operative management of the initial cardiac procedure;
- time to re-operation for mediastinitis, post-operative management and in-hospital survival.

Survival of patients after their discharge from the Nantes CHU was determined by phoning GPs at the beginning of August 2007 and enquiring about the patient's status (alive/deceased), irrespective of the interval between mediastinitis and death.

Causes of death, both in-hospital and after discharge, were listed.

Patient management

All patients received standard surgical management and medical care. Re-operation consisted in mediastinal exploration via a sternotomy under a general anaesthetic. The original sternotomy was re-opened, any fibrin deposits were removed and the skin and underlying tissue debrided. Several swabs were obtained for bacteriological analysis. Non vascularised areas of the sternum were resected with a surgical saw. Finally, the pericardial cavity was cleaned and the mediastinal region abundantly irrigated with 0.5% iodinated povidone. Drains for drainage and irrigation were inserted and, wherever possible, sternal synthesis achieved. Irrigation-drainage was immediately started with saline solution and 0.5% iodinated povidone (100 ml/hour) and was continued for several days with close monitoring of input/output to avoid tamponnade. Irrigation-drainage was only withdrawn once the patient no longer presented with systemic or local signs of sepsis and several consecutive drainage samples were found to be bacteriologically sterile. If it was impossible to close the thorax, a muscle advancement flap was created or, if this also was impossible, then open wound treatment was necessary. Medical care consisted in starting early broad spectrum antibiotics as soon as the diagnosis was reached and post-operative care in the ICU if organ failure arose. The gold standard first line antibiotic treatment in our Institute comprises two antibiotics with known efficacy against *Staphylococcus aureus* and coagulase-negative staphylococci. Antibiotics were initially administered intravenously as a combination of an aminoside (gentamicin) and a glycopeptide (vancomycin). The drugs administered were adjusted as required once the causal bacteria had been identified and antibiotic susceptibility testing completed. Patients received six weeks of antibiotics with possible follow-on treatment with an oral antibiotic if no signs of systemic sepsis were observed and after discussion of the case at the weekly multi-disciplinary staff meeting. If necessary, patients with haemodynamic, respiratory, renal, liver or hematological failure were treated in the ICU. Patients who did not have organ failure subsequently were treated in the hospital's heart surgery department. After their discharge from hospital, most patients were admitted to a readaptation centre for three weeks before returning home.

Statistical analysis

Data were processed and analysed with Excel and Systat software. Continuous variables were expressed as the mean and standard deviation or median. Qualitative data were expressed as the absolute value and/or percentage. Univariate analysis was performed on the quantitative variables using the Student *t*-test or Mann-Whitney test and on the qualitative variables using the Chi^2 test of Fisher's exact test. Variables with $P < 0.1$ in the univariate analysis were included in a logistic regression model to determine the independent factors associated with death. Model calibration was tested using the Hosmer-Lemeshow test. Time to onset of death was measured via Kaplan-Meier type survival analysis.

Results

Patient characteristics

During the period covered by this study, 5574 patients underwent cardiac surgery, 39 of which developed mediastinitis, i.e. an overall incidence of 0.7%. History of the first operation and peri-operative characteristics for all patients are shown in Tables 1 and 2. None of the factors studied was associated with a risk of mortality. Twenty-eight (28) patients or 72% of the cases of mediastinitis, underwent coronary bypass surgery (CBS) both with and without valve replacement, i.e. an incidence of 1.1% during the study period. Twenty-three patients (59%) had undergone CBS with grafts of one or two mammary arteries. Eleven patients (28%) required early re-operation (within 72 hours). The mean interval between the first intervention and re-operation for mediastinitis was 21.4 ± 15 days (median = 18 days; 5th percentile = 4.95; 95th percentile = 49.80). Irrigation lasted a mean of 9.2 ± 5 days (median = 9 days; 5th percentile = 7.50; 95th percentile = 13.45) and drainage, a mean of 13 ± 5 days (median = 12 days; 5th percentile = 10.20; 95th percentile = 15.84) for all patients. The peri-operative characteristics during surgery for mediastinitis are shown in Table 3.

Microbiological documentation

Three cases of mediastinitis were not documented. Of the documented cases, 34 involved a single bacteria and two were polymicrobial involving *Staphylococcus aureus* and an enterobacteria. Of the 38 bacteria isolated, staphylococci were predominant: methicillin-sensitive *Staphylococcus aureus* (21), coagulase-negative *Staphylococcus aureus* (10) and methicillin-resistant *Staphylococcus aureus* (1). Of the other bacteria, five enterobacteria (*Enterobacter aerogenes, Enterobacter cloacae, Escherichia coli, Serratia marcescens* $\times$ 2) and a *Pseudomonas aeruginosa* were isolated.

Twenty-four patients (62%) had positive hemocultures obtained during treatment of mediastinitis, with methicillin-resistant *Staphylococcus aureus* in 71% of cases; this complies with the results obtained for samples obtained per-operatively.

Table 1 Demographic data, history and death risk in patients with mediastinitis between April 2002 and July 2006 ($n = 39$).
Données démographiques, antécédents et risque de décès des patients ayant développé une médiastinite entre avril 2002 et juillet 2006 ($n = 39$).

Variables	Patients		*P*
	Surviving ($n = 31$)	Deceased ($n = 8$)	
Obesity	15 (48.4%)	4 (50%)	1.00
Diabetes	10 (32.2)	3 (37.5)	1.00
Smoking	16 (51.6)	4 (50)	1.00
Chronic obstructive bronchopulmonary disease	5 (16.1)	2 (25)	0.61
Arteriopathy	8 (25.8)	4 (50)	0.22
Corticosteroid therapy	3 (7.7)	1 (12.5)	1.00
Left ventricular ejection fraction < 40%	12 (9.7)	5 (62.5)	0.26
ASA score 3	19 (61)	6 (75)	0.68
ASA score 4	12 (39)	2 (25)	0.68
Mean age (years) ± standard deviation	62.5 ± 12.6	62 ± 14.5	0.92
Mean body mass index ± standard deviation	29.0 ± 3.8	28.9 ± 3.7	0.88

ASA: American Society of Anesthiologists.

Co-infections

Thirteen patients presented with a co-infection, either simultaneously (4) or as a result of the mediastinitis (9), with a mean time to onset of 7 ± 7 with a median time of three days. In order of frequency, these infections were as follows: pneumonia acquired under mechanical ventilation (10), urine infection (1), infectious thrombophlebitis (1) and endocarditis (1). The primary causative bacteria were *Staphylococcus aureus* (6) and *P. aeruginosa* (3). In four cases, methicillin-sensitive *Staphylococcus aureus* was responsible for the co-infection and mediastinitis. The three *P. aeruginosa* respiratory infections arose in heart transplant patients.

Mortality rates

By August 1st 2007, a total of eight patients had died during the period studied, i.e. an incidence of 20.5%. Five patients died in-hospital (12.8%), with one death aris-

Table 2 Peri-operative data for the initial surgical operation and risk of death in 39 patients with mediastinitis between April 2002 and July 2006.
Données périopératoires de l'intervention chirurgicale initiale et risque de décès des 39 patients ayant développé une médiastinite entre avril 2002 et juillet 2006.

Variables	Patients		*P*
	Surviving ($n = 31$)	Deceased ($n = 8$)	
Type of surgery			
Coronary bypass	19 (61%)	4 (50%)	0.69
Valve	3 (9.7)	1 (12.5)	1.00
Valve + coronary bypass	4 (13)	1 (12.5)	1.00
Heart transplant	3 (9.7)	1 (12.5)	1.00
Other	2 (6.7)	1 (12.5)	0.51
Emergency surgery	9 (29)	5 (62.5)	1.11
Duration of surgery > 240 min[a]	14 (45)	5 (63)	0.45
Number of mammary grafts if coronary bypass			
One internal mammary artery	16 (52)	3 (38)	0.69
Two internal mammary arteries	2 (6.5)	2 (25)	0.18
Duration of hospitalisation in Intensive Care > 48 hrs	16 (51)	6 (75)	0.42
Duration of mechanical ventilation > 24 hrs	5 (16)	2 (25)	0.61
Amines required in ICU	16 (52)	6 (75)	0.42
Early surgical re-operation (< 72 hrs)	9 (29)	2 (25)	1.00
Mean duration of ECC (min)	94 ± 70	133 ± 72	0.17

[a] 75th percentile of the usual duration of a surgical intervention at the Nantes CHU [1].

Table 3 Diagnostic and peri-operative data after re-operation for mediastinitis and risk of death in 39 patients with mediastinitis between April 2002 and July 2006.
Données diagnostiques et périopératoires après reprise chirurgicale pour médiastinite et risque de décès des 39 patients ayant développé une médiastinite entre avril 2002 et juillet 2006.

Variables	Patients		*P*
	Surviving (*n* = 31)	Deceased (*n* = 8)	
Discharge from sternotomy	26 (83.9)	7 (87.5)	1.00
Positive bacteremia	17 (54.8)	7 (87.5)	0.12
Transfer from ICU possible before re-operation	28 (90.3)	5 (62.5)	0.08
Microbiological strain			
Methicillin-sensitive *Staphylococcus aureus*	15 (48.4)	5 (62.5)	0.69
Methicillin-resistant *Staphylococcus aureus*	1 (3.2)	0	1.00
Coagulase-negative *Staphylococcus aureus*	8 (25.8)	2 (25)	1.00
Gram-negative bacillae	2 (6.5)	1 (12.5)	0.51
Polymicrobial culture	2 (6.5)	0	1.00
Mean interval before re-operation (days)	20.8 ± 13.5	23.7 ± 20.8	0.63
Mean duration of irrigation (days)	9.5 ± 6	8 ± 4	0.51
Mean duration of drainage (days)	12.5 ± 4.8	15.4 ± 5.6	1.15

Table 4 Cause of death for the eight patients with mediastinitis between April 2002 and July 2006.
Étiologies des décès des huit patients ayant développé une médiastinite entre avril 2002 et juillet 2006.

	n (%)
In-hospital deaths (*n* = 5)	
Multiple organ failure caused by infection (mediastinitis)	2 (25)
Cerebral anoxia due to heart failure	2 (25)
Gastrointestinal necrosis caused by terminal heart failure	1 (12.5)
Deaths after discharge (*n* = 3)	
Terminal heart failure	1 (12.5)
Serious pancreatitis	1 (12.5)
Sudden death of unknown origin in the home	1 (12.5)

ing within 30 days, i.e. a mortality rate at one month of 2.6%. The three-month and one-year mortality rates were 15.4 and 7% respectively. One patient died 598 days after mediastinitis was diagnosed. The main cause of death was heart failure. Two patients died as a direct result of their methicillin-sensitive *Staphylococcus aureus* mediastinitis (Table 4). A Kaplan-Meier survival curve was plotted (Fig. 1). The mean survival time was 505 days. Survival was 97 ± 2% after 30 days, 90 ± 5% after 60 days, 82 ± 6% after 218 days, and 79 ± 7% after 598 days. There were no deaths between the 218th day and the 598th day. The one-year survival rate was 82%. Three patients died within a maximum of 298 days after leaving the hospital.

Risk factors for mortality

In the univariate analysis, three factors identified in the post-operative period were significantly associated with death: co-infection (OR = 10.3, 95% confidence interval [$IC_{95\%}$] = 1.4 — 97.2, $P = 0.01$), prescription of an amine required (OR = 6.3, $IC_{95\%}$ = 1.0 — 18.7, $P < 0.045$) and time spent in intensive care before onset of mediastinitis (29 days versus 18 days, $P = 0.009$). In the logistic regression mulit-variate analysis, only the presence of a co-infection was

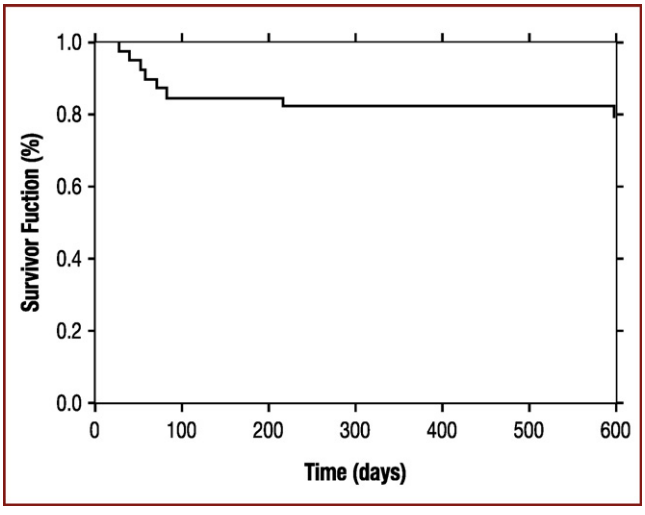

Figure 1. Kaplan-Meier survival curve, expressing the probability of survival in percent (x-axis) versus time (y-axis).
Courbe de survie par estimation de Kaplan-Meier, exprimant la probabilité de survie en pourcentage (ordonnée) en fonction du temps en jours (abscisse).

an independent factor related to death (OR = 13, 95% $IC_{95\%}$ = 1.1 — 156, P = 0.043). Calibration of the model was satisfactory (P = 0.19). The instantaneous risk of death was seven times higher in patients with a co-infection versus those without infection (regression coefficient = 1.973, or $e^{1.973}$ = 7.19).

Discussion

Patients treated for mediastinitis are at higher risk of morbidity and mortality than patients who do not experience infectious complications [2,6]. In our cohort of 39 patients presenting with mediastinitis at the Nantes CHU between 2002 and 2006, the in-hospital mortality rate was 12.5% and survival at one year was estimated to be 82%. Mortality and survival are two facets of a single event observed at different times. Mortality estimates are often given for different times during treatment (mortality in the reanimation ward, at three months, at one year, etc.) for patient populations which are not always comparable. The mortality rates reported in the literature can therefore range from 11 to 20% including either patients undergoing re-operation for sterile sternal dehiscence or patients who have already presented with failure of one or more organs whilst in the ICU [6,7,10].

Although mediastinitis is an infection, in most cases death does not occur as a result of uncontrolled infection. In our cohort, only two patients died in-hospital as a direct result of infection through multiple organ failure and septic embolism. The three other in-hospital deaths were the result of heart failure, which caused either massive gastrointestinal necrosis or untreatable cerebral lesions. There was no single cause of death outside the hospital (terminal heart failure, pancreatitis). In sum, half of the deaths arising both within and outside the hospital were caused by terminal heart failure. In addition, pre-operative changes in the left ventricular ejection fraction were not a risk factor for death. Mediastinitis seemed to render already vulnerable patients even more fragile from a cardiac point of view although this was impossible to quantify at the time they were being treated.

Little is reported about causes of death in the literature. In the study conducted by Trouillet et al. in the reanimation ward, 60% of deaths were the result of primary or secondary infection [9]. This percentage is no doubt an overestimation since only deaths arising in the ICU are taken into account, unlike our study which observed death rates over a longer period of time. Estimates of mean and long-term survival rates are difficult to compare. The one-year survival rate in the study involving a series of 193 cases of mediastinitis was estimated to be 78% [11], which is similar to the rate found in our study. In another study conducted on 183 cases of mediastinitis, the estimated one-year survival rate was lower at 67% [12]. This excess mortality was observed after two and five years in three studies comparing cardiac surgery patients presenting with and without mediastinitis [2,6,7]. Survival rates after treatment for mediastinitis are still difficult to compare between studies given disparities in the inclusion and exclusion criteria employed. The size of our cohort, and thus the lack of power of the analysis, may have masked the role played by of some of the factors studied.

Our results show that the onset of a second infectious disease or co-infection with mediastinitis, is an independent risk factor for mortality. The associated condition was pneumonia in 77% of cases which resulted in a prolongation of mechanical ventilation and thus an increase in the time spent in intensive care. This raises the question of whether the infection was transmitted by bacterial translocation or bacteremia from the mediastinitis or conversely, whether the mediastinitis could be secondary to the pneumonia. The second hypothesis appears unlikely, since the co-infection was diagnosed during re-operation for mediastinitis (median three days). In our study, the bacteria identified were staphylococci in 77% of cases. *Staphylococcus aureus* was identified in 54% of cases of mediastinitis with only one methicillin-resistant strain observed. The bacteria causing pneumonia were different from those responsible for mediastinitis except in four cases in which methicillin-sensitive *Staphylococcus aureus* was isolated at the two sites of infection. Given the proportion of methicillin-sensitive *Staphylococcus aureus* mediastinitis cases in our cohort, the incidence of nasal carriage reported in the literature and the pathogenicity of this bacteria, systematic screening for *Staphylococcus aureus* and local nasal treatment with mupirocin could be integrated into surgical wound infection prevention strategies after heart surgery [13—16].

However, in view of the relatively small size of our population, these results are to be interpreted with caution, despite the fact that the study covers a period of six years. The logistic regression modelling measurement of the estimated co-infection rate (OR) calculated in our population is not precise owing to the 95% confidence interval values. Analysis of the causal relationship between onset of co-infection in patients who developed mediastinitis and death must be validated in a more powerful, multicentre study involving more cases of mediastinitis, to confirm our hypothesis.

In conclusion, the mortality rate varied as a function of survival time and mediastinitis was not the main cause of death. The risk factors for onset of mediastinitis do not appear to be the same as those for mortality. However, co-infections arising subsequent to mediastinitis could increase the risk of death in patients presenting with other organ failures or altered cardiac function, without being the direct cause of death.

Conflicts of Interests

None.

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